AUSTIN HYL INGN:019

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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/459,713	06/02/95	ZHANG	INGN:019 W UTSC.466/HYL

EXAMINER
GUZO, D

ART UNIT	PAPER NUMBER
1805	7

18N2/0509

ARNOLD WHITE AND DURKEE
P O BOX 4433
HOUSTON TX 77210

DATE MAILED: 05/09/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire three (3) month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☑ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 9-13 and 22-27 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 9-13 and 22-27 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

Response
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BY Cru
ENTD. BY DF

P23589
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REC'D A.W.D.
MAY 13 1996
DOCKET DESK

EXAMINER'S ACTION

TO SEPARATE, HOLD TOP AND BOTTOM EDGES, SNAP–APART AND DISCARD CARBON

FORM PTO-892 (REV. 2-92) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	SERIAL NO.	GROUP ART UNIT	ATTACHMENT TO PAPER NUMBER
NOTICE OF REFERENCES CITED	08/459713	1805	7
	APPLICANT(S) ZHANG ET AL.		

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	A						
	B						
	C						
	D						
	E						
	F						
	G						
	H						
	I						
	J						
	K						

FOREIGN PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUB-CLASS	PERTINENT SHTS. DWG	PERTINENT PP. SPEC.
	L								
	M								
	N								
	O								
	P								
	Q								

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

!	R	"Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy" S.H. Orkin and Arno G. Motulsky, Co-chairs, Published 12/7/95.
	S	
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EXAMINER	DATE
David Prouty	5/6/96

* A copy of this reference is not being furnished with this office action.
(See Manual of Patent Examining Procedure, section 707.05 (a).)

1. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

2. Claim 13 is rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Applicants recite a method for restoring wild-type p53 function to a cell (in a mammal) deficient in wild-type p53 protein, said method comprising contacting the cell with a recombinant adenovirus containing the p53 gene and wherein said vector is capable of expressing the p53 gene in an amount effective to express wild-type p53 in the cell. Applicants' method, as can be determined from the specification, is a gene therapy method for treating human diseases associated with mutations or defects in the p53 gene. It is noted that while applicants broadly recite a method for restoring p53 function in mammals, applicants have not disclosed how the skilled artisan would use a gene therapy method for restoring p53 function in a mammal such as a nude mouse or indeed, any mammal other than a human.

The test of enablement is whether one skilled in the art could make and/or use the claimed invention from the disclosures in the application coupled with information known in the prior art without undue experimentation. United States v. Teletronics Inc., 8 USPQ2d 1217 (Fed. Cir. 1988). In determining enablement, it is for the invention as claimed that enablement must exist. Whether undue experimentation is needed is not based upon a single factor, but rather a conclusion reached by weighing many factors. Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986). Said factors include the following:

1) State of the art. Applicants' invention pertains to the gene therapy art. The state of the art, at the time of applicants invention was extremely poorly developed. Indeed, even today the gene therapy art is in its' infancy. The state of the art is exemplified by the "Report and Recommendations of the Panel to Assess the NIH Investments in Research on Gene Therapy" (Published Dec. 7, 1995) wherein it is noted that "Efficacy has not been established for any gene therapy protocol." (Page 13) and with regard to gene therapy treatments for cancer, that "Daunting hurdles must be overcome if gene correction strategies are to achieve a meaningful clinical outcome." (Page 6). The "Report" also indicates that adenoviral vectors are potentially dangerous for use in humans because several adenoviral genes have been shown to influence tumor formation in experimental animals and are associated with malignant transformation of cells in culture and that in regard to cancer, that the relevance of

animal models to human disease conditions is unclear and that in gene therapy experiments for cancer, "...better measures of biological activity are needed." (Page 34). It is again noted that the above statements represent the state of the art currently and that the art at the time of applicants' invention was considerably less developed.

2) Unpredictability of the art. The gene therapy art is extremely unpredictable. This unpredictability is manifested in the inability to achieve any clinically significant results in patients, the inability to regulate gene expression in transformed cells *in vivo*, the inability to maintain expression of the introduced gene in cells *in vivo* for significant periods, the inability to exclude tumorigenic effects from use of recombinant adenovirus vectors, the inability to even determine the biological activity of the gene therapy techniques, the inability to develop animal models which are predictive of the corresponding disease condition in humans, etc.

3) Number of working examples. Applicants provide no working examples of the claimed method in humans. Applicants do provide an *in vivo* example of the claimed method in nude mice; however, it is noted that applicants have not taught the skilled artisan how to use a method for restoring p53 function in mice and that the relevance of this animal system to any human disease condition is unclear.

4) Breadth of the claims. Applicants claims read on a method of treating any mammal (this reads on thousands of different species) by restoring p53 function.

5) Amount of guidance by applicants. Applicants present no teachings sufficient to overcome the art recognized problems associated with gene therapy techniques in humans, i.e. see for example the problems associated with extrapolating the results of animal models to humans, the problems encountered with actual clinical gene therapy studies (Page 14), the lack of efficacy in any gene therapy protocols, the high mutation rate in cancer cells and the likelihood that mutations in the introduced p53 gene will arise in some cells, leading to a re-outgrowth of cancer cells, etc.

6) The nature of the invention. The invention relates to gene therapy, one of the most complex, undeveloped and unpredictable areas in molecular biology.

For the above reasons, it must be considered that the skilled artisan would have needed to have practiced undue and excessive experimentation in order to practice the claimed invention and to overcome daunting problems which, years after the filing date of the priority application, remain unsolved.

3. Claims 9-12 and 22-27 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited a method of restoring p53 function in cells *in vitro*. See M.P.E.P. §§ 706.03(n) and 706.03(z).

Applicants broadly recite a method for expressing wild-type p53 protein in cells, wherein the cells could be *in vitro* or *in vivo*. However, for the reasons outlined in the above 35 USC 112, 1st paragraph, enablement, rejection of Claim 13, the claims are enabled only for a method for restoring p53 function in cells *in vitro* and are not enabled for a method of restoring p53 function in cells *in vivo*.

4. Claims 9-13 and 22-27 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 (and dependent claims) are vague in the recitation of the phrase "...comprising an expression region encoding p53...", (this language is also present in Claims 22 and 23). It is unclear what applicants mean by "an expression region", i.e. does this language encompass the p53 gene or the p53 gene plus some other undefined regions associated with the p53 gene, etc. Claim 9 is unclear in the recitation of the phrase "...vector capable of expressing...". The capacity of a compound or composition to perform some function carries no patentable weight, is merely a statement of a latent characteristic and is not proper claim language. Claim 9 is vague in that in lines 1-2, applicants claim a method for restoring p53 function "...to a cell (emphasis added) deficient in wild-type p53..." but then in line 4, applicants recite a vector capable of expressing p53 in

human malignant cells; therefore the scope of the claim, with regard to what cells are encompassed by the claim, is uncertain. Claim 9 is vague in that applicants recite a vector capable of expressing p53 "...in an amount effective to express wild-type p53 in the cell."; it is unclear what level of p53 is being expressed, i.e. are applicants claiming expression of a level of p53 sufficient to block the growth of malignant cells?

Claim 25 is vague in that applicants recite a recombinant adenovirus with the structure of Fig. 1. However, Fig. 1 does not disclose a recombinant adenovirus, but only an outline of the process by which a recombinant adenovirus can be generated by recombination between recombinant plasmids.

With regard to the IDS submitted 7/31/95, the references cited therein have not been considered because the examiner has not been able to locate the references in the 07/960,513 parent application.

No claims are allowed.

Certain papers related to this application may be submitted to Art Unit 1805 by facsimile transmission. Papers should be faxed to Art Unit 1805 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (Nov. 16, 1993) and 1157 OG 94 (Dec. 28, 1993) (See 37 CFR 1.6(d)). The Art Unit 1805 fax number is (703) 308-0294. NOTE: If applicants do submit a paper by fax, the original signed copy should be retained by applicants or applicants' representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo whose telephone number is (703) 308-1906. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mindy Fleisher, can be reached on (703) 308-0407. The fax phone number for this Group is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

DAVID GUZO
PATENT EXAMINER
GROUP 1800

David Guzo
May 6, 1996

Applicants' Copy

 #4

Form PTO-1449 (modified)

List of Patents and Publications For Applicant's Information Disclosure Statement

(Use several sheets if necessary)

ATTY. DOCKET NO. UTSC:466/HYL; INGN:019	SERIAL NO. 08/459,713
APPLICANT Wei-Wei Zhang and Jack Roth	RECEIVED AUG 14 1995
FILING DATE Jnue 2, 1995	GROUP ~~1806~~ 1805 GROUP 1800

U.S. PATENT DOCUMENTS

EXAM. INIT.	REF. DES.	DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	FILING DATE IF APPROPRIATE

FOREIGN PATENT DOCUMENTS

EXAM. INIT.	REF. DES.	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB CLASS	TRANSLATION YES/NO
	B6	WO 93/03769	MAR 4, 1993	PCT			
	B7	FR 2,688,514	SEP 17, 1993	France			
	B8	WO 94/10323	MAY 11, 1994	PCT			
	B9	WO 94/24297	OCT 27, 1994	PCT			
	B10	WO 95/02697	JAN 26, 1995	PCT			

OTHER ART (Author, Title, Journal, Volume, Pertinent Pages, & Date)

	C62	Casey *et al.*, "Growth Suppression of Human Breast Cancer Cells by the Introduction of a Wild-Type p53 Gene," *Oncogene*, 6:1791-1797, 1991.
	C63	Wills and Menzel, "Adenovirus Vectors for Gene Therapy of Cancer," *Journal of Cellular Biochemistry*, p. 204, Abstract # S216, March-April 1993.
	C64	Zhang *et al.*, "Generation and Identification of Recombinant Adenovirus by Liposome-Mediated Transfection and PCR Analysis," *BioTechniques*, 15(5):868-872, 1993.
	C65	PCT Search Report dated July 5, 1995.

EXAMINER David Fitzpatrick DATE ~~CONSIDERED~~ 5/6/96

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.